Cancer Chemother Pharmacol (1986) 18 (Suppl 2): S 30–S 33

Cancer Chemotherapy and Pharmacology

Ifosfamide by bolus as treatment for advanced non-small cell lung cancer

N. Thatcher[1], H. Anderson[1], D. B. Smith[1], W. P. Steward[1], K. Webb[2], A. Hilton[3], and A. Rahman[3]
From the Manchester Lung Tumour Group

[1] Cancer Research Campaign, Department Medical Oncology, Christie Hospital and Holt Radium Institute, Manchester, England
[2] Department of Thoracic Medicine and Surgery, Wythenshawe Hospital Manchester, England
[3] Department of Medicine, North Manchester General Hospital Manchester, England

Summary. Ifosfamide at 5 g/m^2 was given as a bolus to 48 patients with advanced progressing non-small cell lung cancer. Mesna (5 g/m^2) was also given with the ifosfamide, both over 30 min. Further mesna was then given p.o. (3 g/m^2) at 4, 8, and 12 h. If oral mesna was not acceptable then one or, if necessary, two 4-h to 6-h infusions (3 g/m^2) were administered. A maximum of six courses at 3-weekly intervals was prescribed.

A total of 174 courses was administered, and oral mesna was given during 64 courses: discharge was considered possible within 8–10 h after 55% of courses.

Haematological toxicity was mild and no renal dysfunction was noted. Two patients became drowsy shortly after ifosfamide, but recovered 24–36 h later.

The objective response rate was 29%, with one complete responder. A further 31% of patients (symptomatic responders) with stable disease symptomatically improved after the chemotherapy, by 20 or more points on the Karnofsky scale. The median survival was 5 months for the whole group, and 8 months each for the objective and symptomatic responder groups. Most patients' Karnofsky and respiratory scores improved with the chemotherapy. Ifosfamide with mesna can be given by short infusions, and the mesna given p.o. prevents any urothelial toxicity. Further exploration of short-infusion ifosfamide and mesna therapy would reduce hospitalization and allow for day-case regimens.

Introduction

Ifosfamide given as a single agent has shown activity against non-small cell carcinoma with an overall response rate of 31% [4]. The ifosfamide was generally given by infusion or as a fractionated dosage regimen to overcome the major problem of haemorrhagic cystitis [1–4, 7]. Some short-infusion, bolus administration of ifosfamide has been conducted previously with doses of 4 g/m^2, but this required continual bladder washout to prevent the cystitis [3, 7].

Since the development of mesna, a uroepithelial protective agent, the side-effect of haemorrhagic cystitis has been completely absolished [2, 4]. It was therefore decided to investigate the efficacy of single bolus doses of ifosfamide (at 5 g/m^2) with mesna in advanced non-small cell lung cancer patients. Bolus doses would avoid lengthy hospitalization, and possibly allow for a day-case regimen and greater flexibility of use in the future.

Offprint requests to: N. Thatcher, CRC Department Medical Oncology, Christie Hospital and Holt Radium Institute, Manchester M20 9BX, England

Materials and methods

Patients. Forty-eight patients with advanced histologically proven non-small cell lung cancer and progressive disease were studied. All patients were inoperable because of tumour extent and were not considered suitable for palliative radiotherapy. Patients with evidence of central nervous system metastases, those with a Karnofsky score of less than 30 or greater than 70, and those aged over 70 years were not eligible for the study.

There were 30 male and 18 female patients, with a median age of 59 years (range 33–70). The stage was "limited", i.e. confined to one hemithorax, with or without ipsilateral supraclavicular nodes, in 46% of patients and extensive in the remaining 54%. Other clinical and pathological details are given in Table 1.

Treatment. Ifosfamide 5 g/m^2 with the same dose of mesna was given over 30 min. in 500 cm^3 normal saline. Three further doses of mesna (3 g/m^2) were given p.o. in fruit juice at 4-h intervals, 4, 8 and 12 h after the start of the ifosfamide infusion. The mesna dose was given as one or two consecutive 6 h infusions if the oral doses were not tolerated. If patients were particularly nauseated (often anticipatory) shortly after the end of the ifosfamide bolus then the first mesna infusion was started at about 2 h, rather than delaying until the 4 h oral dose was due. Metoclopramide 100 mg i.v. was given immediately before and 3 h after the ifosfamide. A maximum of six courses of treatment was given, with a 21-day interval between treatment cycles.

Before each course of treatment the patients were assessed with reference to routine history, clinical examination. Karnofsky and respiratory scores [5], blood count, biochemistry, chest X-rays, and appropriate scans when clinically indicated. If the white count was less than 2500 cells/μl and/or the platelet count was less than 75000/μl therapy was delayed by 1 week or until recovery to above these levels (checked weekly). If the disease progressed the treatment protocol was discontinued and symptomatic measures, including appropriate radiotherapy, were instituted.

Table 1. Clinical and pathological features

Weight loss (10% over previous 6 months)		73%
Karnofsky score	50	46%
	50–70	54%
Respiratory score[a]	4	44%
	4, 5	56%
Elevated enzymes	AP	52%
	LDH	35%
	GGT	19%
Histology	Squamous	52%
	Large cell	12%
	Adenocarcinoma	26%
	Undifferentiated (non-small cell)	10%
Metastases	Lymph nodes: Neck, supraclavicular	29%
	Other	13%
	Effusion	25%
	Pulmonary (contralateral)	10%
	Liver	17%
	Bone	14%
	Skin	13%
	Other (pericardial, soft tissue, marrow, etc.)	21%
Interval from diagnosis to chemotherapy median (range) (months)		1 month (1–23)

AP, Alkaline phosphatase; LDH, lactate dehydrogenase; GGT, gamma glutamyl transpeptidase

[a] Respiratory score see Ref. [5]

Follow-up. After the end of the last course of treatment patients were seen monthly for 4 months and then every 3 months for 1 year and every 6 months thereafter. Routine blood counts and chest X-rays were repeated at each visit. More frequent or additional investigations were done as clinically indicated. Assessment for evidence of objective response was undertaken at the first follow-up visit (1 month after the last course of chemotherapy) and determined by standard UICC criteria [6]. Toxicity, Karnofsky performance and respiratory scores [5, 6] were recorded after each course of chemotherapy and 1 month after the final treatment. The minimum follow-up is now 9 months.

No patient has been excluded from analysis because of incomplete treatment, early death, toxicity, etc.

Results

The objective response rate was 29%, including one patient (2%) who obtained a complete response. A further 31% of patients were classed as "symptomatic" responders. Symptomatic response was defined as stable disease together with a Karnofsky score increase by 20 or more during the response evaluation period. Of those patients who had an objective response, 83% attained response within three courses of chemotherapy, and the corresponding proportion of subjective responders was 89%. Progressive disease was noted in 25% of the patients, and stable disease without symptomatic improvement in 13%, the remaining 2% representing one possible treatment-related death. The median duration of response was 5 months (range 1–10 months) and the details of the responding patients' tumours, with stage and histology for each, are given in Table 2. Among the 14 objective responders, 6 have not relapsed.

Disease recurred in previous treatment sites in 56% of the patients who responded and in new sites in 16%; in the remaining 28% relapse occurred in both pretreatment and new sites. Tumour relapse occurred within the thorax in 46% of patients, in distant sites in 23%, and in both areas in 31% of the patients who initially responded. The numbers of patients relapsing in individual metastatic sites is given in Table 3.

Survival

The median survival for the total group was 5 months (range 1–14 months), and 14 patients are still alive. There were no statistically significant differences in survival among the four histological types ($P = 0.23$ log rank chi-square analysis) or in stage of tumour ($P = 0.11$). The median survival in the objective responder patient group was 8 months (range 1–12) months and was not significantly different ($P = 0.75$) from the survival in the symptomatic responder group, with median 8 months (range 1–14 months). However, the survival of non-responding patients (median 2, range 1–7 months), including those with static (median 4, range 1–9 months) and those with progressive disease (median 1, range 1–7 months) is significantly different $P = 0.003$ from that of the responder groups (see Fig. 1). The median survival from relapse was 2 months (range 1–7 months).

Table 2. Clinical features of responder patient group

	Histology			
	Squamous	Large cell	Adenocarcinoma	Undifferentiated
Patients	25	5	13	5
Stage				
Limited	1 (4)	2 (–)	– (4)	2 (–)
Extensive	5 (5)	– (–)	3 (2)	1 (–)

Objective response, 14 patients; symptomatic response, number in ( ), 15 patients

Sites of objective response

Five patients with limited stage disease responded: mediastinum, primary tumour all patients; neck nodes 3 patients; pleural effusions 2 patients

Nine patients with extensive stage disease responded: mediastinum, primary tumour 8 patients, neck nodes 2 patients, other nodes 5 patients, contralateral lung 1 patient, pleural effusions 1 patient, liver 4 patients. Other sites (pericardium) 1 patient

Table 3. Relapse sites

Site	Number of patients with relapse or recurrence
Primary tumour	16
Mediastinum	17
Contralateral lung/Effusion	8
Nodes	8
Liver	4
Bone	8
Soft tissue	2
Brain	2
Other	4

Some patients had multiple sites of relapse

Toxicity

A total of 174 courses of chemotherapy were administered, with a median of 3 courses per patient: 13% of the patient group received only the first course and 33% all six courses. The second course of chemotherapy was delayed in 10% (five patients), the third course was delayed in 4% (two patients), the fourth course in 8% (four patients) and the fifth and sixth courses each in 2% (one patient), a total of 13 occasions.

Oral mesna was given in 64 courses (37% of the total number) and discharge within 8–10 h was considered possible after 55% of courses; the difference was accounted for by patients who received only the first 6-h mesna infusion.

Haematological toxicity for each course is given in Table 4. In only a minority of patients was there moderate or serious toxicity: the frequency of blood transfusion and administration of antibiotics was low. It should be noted that antibiotics were given whenever there was the slightest likelihood of infection, and in most cases bacteriological confirmation was not obtained. There was one possible treatment-related death from infection, in a patient whose leucocyte count was greater than 3000 cells/μl. There was no platelet toxicity of grade 2 or more, and renal function was not compromised. Mild cystitis occurred during 4% of all courses. Two patients developed mental confusion and drowsiness lasting 1–2 days shortly after receiving ifosfamide. Nausea and vomiting was severe during 2% courses and moderate during 28%, while for 5% of courses no nausea nor vomiting was noted; in the remainder nausea alone, lasting less than 24 h, was recorded.

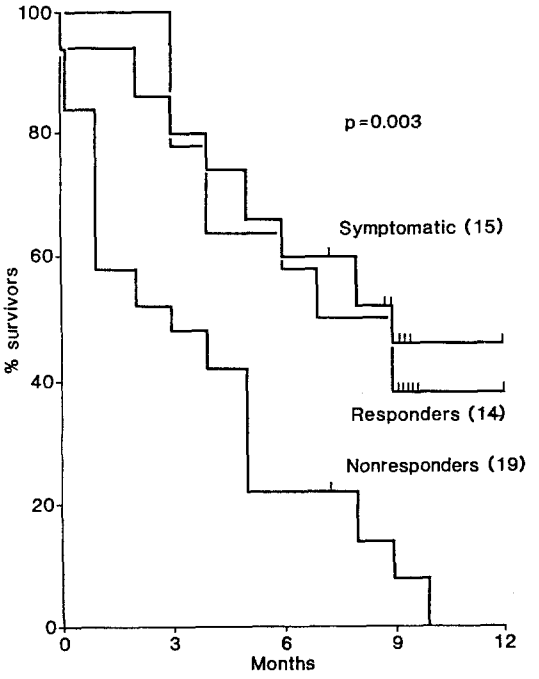

Fig. 1. Survival in responders and non-responders

An important feature of the study was the improvement in the Karnofsky and respiratory scores noted after the last course of chemotherapy (Table 5). At the end of treatment a Karnofsky score of greater than 70 was recorded in 29% of all the patients, as against none with this score before treatment; a similar change occurred when breathlessness (the respiratory score) was assessed, with a change from 2% to 29% at the end of treatment.

Discussion

Few reports exist on the effects of chemotherapy for non-small cell lung cancer on the patients' quality of life, performance status, or change in symptoms as a result of treatment [1]. In general, modern combination chemotherapy, often including *cis*-platinum, has produced a modest increase in response rates over those obtained with earlier combination regimens or single agents, but there has been no clear survival benefit [1, 8, 9].

A major problem in assessing the value of chemotherapy for non-small cell lung cancer concerns the

Table 4. Haematological toxicity per course

Course no.	1		2		3		4		5		6	
Number patients	48		41		27		22		18		16	
Toxicity grade	2	3	2	3	2	3	2	3	2	3	2	3
Hb	4	–	2	–	1	–	2	–	1	–	1	–
WBC	1	1	2	1	1	1	1	–	–	1	1	–
	*	**	*	**	*	**	*	**	*	**	*	**
BTs	–	2	1	1	1	–	–	1	–	1	–	–
	i.v.	p.o.	i.v.	p.o.	i.v.	p.o.	i.v.	p.o.	i.v.	p.o.	i.v.	p.o.
Antibiotics	1	5	4	2	–	1	–	4	–	1	–	1

Blood transfusions: *2 units; **3 units

Table 5. Change in patient's Karnofsky performance scores and respiratory scores with treatment

	Before	After
KPS		
≤50	71%	38%[a]
60, 70	29%	33%
70+	–	29%
RS		
1, 2	2%	29%
3	42%	46%
4,5	56%	25%[a]

RS Grade 1, 2: patients car climb hills, stairs, walk any distance on the flat at normal pace, without dyspnoea; grade 3: can walk more than 100 yards at own speed without dyspnoea; grade 4: dyspnoea on walking 100 yards or less; grade 5: dyspnoea on mild exertion, e.g., undressing (dying patients included)

[a] Includes patients who died

heterogeneity of treatment populations. In our present study it is important to stress that the patients were symptomatic at the start of treatment with a Karnofsky performance in the middle ranges. In addition, their tumours were known to be progressing at the start of chemotherapy. Therefore, patients in a "stable growth phase" of their tumour were not included in the study, which may account for the somewhat disappointing median survival of 5 months. However, 29% of patients are still alive at 6–14+ months.

An encouraging feature of this single-agent study was the improvement in the patients' symptoms, which became obvious when the Karnofsky and respiratory scores were assessed before and at the end of treatment. Although the complete response rate was negligible, it appears that the majority of patients did benefit from the treatment in terms of symptom relief. Another important feature of the study was the ability of the experienced nursing staff to respond quickly and anticipate patients' problems, thereby reducing treatment toxicity. The main problem with the oral mesna was the unpleasant odour and taste; if this could be overcome then further reduction in the length of hospitalization could be feasible. When the study started the dose and frequency of mesna administration needed to protect against the 5 g/m^2 bolus doses of ifosfamide were uncertain. The mesna dosage described proved quite adequate in preventing bladder toxicity, and it would now appear possible to reduce the dose or frequency of mesna further.

In conclusion, further treatment schedule manipulation would make it possible to give short infusions of ifosfamide and mesna over, for example, 2–3 h, followed by oral mesna, thereby increasing the flexibility of ifosfamide use and allowing day-case regimens.

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